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Editorial

Prognostic Factors for Advanced Seminoma—a Solid Basis for Clinical Trials

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ALTHOUGH A rare malignancy with an incidence of 5–10/100 000, testicular cancer is the most common malignancy in young males of 20–40 years with a steadily increasing frequency in Western industrial countries. Approximately half of these tumours are seminomatous testicular cancer which are well recognised to be biologically different from non-seminomatous testicular cancer (NSGCT). Seminomatous tumours exhibit in particular a less aggressive behaviour in comparison to NSGCT: the growth kinetics are slower, the age peak at presentation is 5–10 years later, the metastatic potential, particularly the risk of blood-born metastasis, is considerably less and interestingly, spontaneous regression with massive lymphocytic infiltration at the site of metastases can occur. As a consequence of this relatively benign biological behaviour, 70–75% of the patients have no clinical detectable metastasis at first presentation and after adjuvant irradiation only 3% develop distant metastases. The majority of the 25–30% of patients with metastatic disease have metastasis confined to the abdominal or—less frequently—mediastinal or supraclavicular lymph nodes; only approximately 15% present with or develop visceral metastatis. Furthermore, seminoma is also generally regarded as highly chemotherapy sensitive, even more than NSGCT. With cisplatin-based chemotherapy, a complete response (CR) rate of 63% and a disease-free survival of 70% in patients with prior irradiation and a CR rate of 71% and disease-free survival of 85% in untreated patients have been reported [5, 6]. Nearly all these data derive from small and often retrospective series, with notable heterogeneity of the patient population, which partially explains the wide range of CR rates from 38 to 100%, progression-free survival rates from 50 to 100% and overall survival rates from 71 to 100% [5, 6]. These large differences in progression-free as well as overall survival and the complete absence of data from prospective randomised trials for advanced seminoma including stratification for potential risk factors, has created for a long time an atmosphere of uncertainty in the scientific community regarding the following questions:

- What chemotherapy could be regarded as standard (PVB, PEB, VIP, PE; three or four cycles etc.)?
- What are the relevant prognostic factors?
- Do all patients with advanced seminoma belong to the group with good prognosis or do all or a certain subgroup behave like NSGCT?
- Should patients with prior irradiation, 'bulky' seminoma, or with tumours of extragonadal origin be treated more aggressively?
- What is the real contribution of etoposide, vinblastine, vincristine, bleomycin or ifosfamide in cisplatin-based combination regimens?
- Is cisplatin-based combination chemotherapy definitively necessary or could it be substituted by single-agent cisplatin or, in recent times, single-agent carboplatin, at least for subgroups?

This uncertainty and different views regarding these questions has led—in contrast to NSGCT—to somewhat different treatment strategies being used for advanced seminomas. Where in the prognostic model established by the Memorial Sloan Kettering Cancer Center [1, 3], all seminomas have been regarded as 'good prognosis' independent of the extent and location of metastasis, other prognostic classifications for advanced germ cell cancer either excluded seminoma (e.g. MRC [11]) or handled seminoma in a manner like NSGCT (e.g. Indiana Classification [2]). Recently, an analysis from the MSKCC of combined data from four consecutive studies in good prognosis testicular cancer (according to the MSKCC criteria) evaluated the predicting factors for clinical outcome [12]. Despite the inferior event-free and overall survival for patients treated with carboplatin/etoposide (35/142 patients) in comparison to VAB 6 or PE, this series was appropriate for prognostic factor analysis since the data represent a single institution's experience generated within sequential prospective trials. Elevation of HCG or LDH have been associated with a significant inferior survival. Also prior irradiation, visceral metastasis and advanced disease (Indiana classification), were associated with a poorer prognosis, although not significant. It was clearly shown that extragonadal or mediastinal seminoma was not associated with a poorer prognosis than seminoma of testicular origin.

Very recently, the International Germ Cell Cancer Collaborative Group (IGCCCG) has reported a prognostic factor analysis of 5202 patients with advanced NSGCT and 660

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patients with advanced seminoma [10]. This meta-analysis included only patients from prospective trials in Europe and U.S.A. treated between 1975 and 1990. In this analysis again extragonadal seminoma was not associated with a poorer prognosis; elevation of HCG was only of borderline significance, whereas elevation of LDH and presence of supraclavicular mass were independent prognostic factors for poorer outcome. The most important adverse prognostic factor was the presence or absence of non-pulmonary visceral metastasis (NPVM). The final prognostic model was mainly developed to separate NSGCT into three different prognostic subgroups with sufficient patients within each subgroup; this model has also been calculated for seminoma and defined two prognostic categories:

- Good prognosis patients without NPVM, independent of HCG or LDH elevation, with a progression-free survival of 82% and a 5 year overall survival of 86%; this group represents 90% of the patients with advanced seminoma.
- The poor prognosis group represents 10% of the patients, and is characterised by patients with NPVM, independent of HCG or LDH level, with a 5-year PFS of 67% and an overall 5-year survival of 72%.

This prognostic model is simple and easy to use and seems to identify a group of patients with a relatively poor prognosis requiring 'better' treatment than standard cisplatin-based combination chemotherapy. However, this model neglects the potential contribution of supradiaphragmatic lymph node involvement and elevation of LDH to define more precisely which individual patient could have a poor prognosis and deserves more treatment.

This model might, therefore, be of limited value for the separation of good from poor prognosis patients in clinical trials which investigate less aggressive treatments in good risk patients and more aggressive treatment protocols—eventually including high-dose chemotherapy—in poor risk patients.

Fossa and associates publish in this issue of the *European Journal of Cancer* (pp. 1380–1387) a separate and much more detailed analysis of a subgroup of 286 patients with advanced seminoma who have been included in the 660 patients of the IGCCCG-prognostic factors analysis [7]. The patients of this subgroup are treated by members of the Medical Research Council of the U.K. The database was much more complete with respect to clinical and laboratory data with possible relevance for prognosis. It is perhaps not surprising but a very sound support for the clinical relevance of the results of this MRC study that the univariate analysis revealed basically the same prognostic factors as reported in the study by Mencel and associates [12] and Mead and associates [10] (Table 1): presence or absence of non-pulmonary visceral metastasis, stage (II versus III versus IV), elevation of LDH, mediastinal or supraclavicular lymph node metastasis presence or absence as well as number of lung metastasis, and prior irradiation. However, elevation of HCG was not a significant predictive factor, in contrast to the MSKCC analysis. Using these factors the authors developed two different prognostic models which are determined by the following factors:

- Stage: II versus III versus IV pulmonary metastases versus IV non-pulmonary visceral metastases.
- LDH: normal versus $< 2 \times$ normal versus $\geq 2 \times$ normal.

Table 1. Comparison of prognostic factors in three recent meta-analyses of metastatic seminoma

	Distribution of patients			5-year survival					
				Progression free			Overall		
	MSKCC	IGCCCG	MRC*	MSKCC	IGCCCG	MRC*	MSKCC	IGCCCG	MRC*
All patients	n=142	n=660	n=286	86%	81%	84%	88%	85%	85%
Primary site									
testis	77%	ne	89%	82%	ne	81%	100%	ne	ne
extragonadal	23%	ne	11%	97%	ne	84%	84%	ne	ne
Number of metastatic sites									
<2	73%	67%	ne	88%	86%	ne	90%	90%	ne
≥ 2	27%	33%	ne	77%	72%	ne	82%	79%	ne
Mediastinal mass									
no	ne	77%	81%	ne	80%	86%	ne	84%	ne
yes	ne	23%	19%	ne	79%	71%	ne	83%	ne
Supraclavicular mass									
no	ne	88%	89%	ne	82%	86%	ne	85%	ne
yes	ne	12%	11%	ne	65%	65%	ne	71%	ne
Visceral non-lung metastasis									
no	94%	89%	88%	87%	81%	86%	90%	85%	ne
yes	6%†	11%	12%	75%†	67%	67%	79%†	72%	ne
Prior irradiation									
no	87%	ne	83%	87%	ne	87%	90%	ne	ne
yes	13%	ne	17%	72%	ne	69%	70%	ne	ne
HCG									
normal	74%	ne	47%	88%	ne	83%	89%	ne	ne
very high	ne	3%	6%	ne	59%	67%	ne	67%	ne

*MRC study: 3-year survival. †Including lung metastases. ne, not evaluable.

These factors allow an easy definition of the prognostic category of an individual patient (Table 2). Model 1 separates the patients into three different prognostic groups with a distinct difference in progression-free survival after 3 years: 97% for the good prognosis group and 86 and 56% for the intermediate and poor prognosis groups, respectively. Model 2 defines one group with good prognosis (94% free from progression at 3 years) and one group with poor prognosis (56% free from progression after 3 years). In both models the difference in prognosis is of clinical relevance.

The authors of this study must be congratulated on this important publication. The information from their study is of high value and essential for the development of a risk-adapted chemotherapeutic strategy in patients with metastatic seminoma. The large differences in progression-free and overall survival between the different reported phase II trials [5, 6] are now better understandable and rather attributable to differences in the patient populations than in efficacy of the treatment protocols used. This is also reflected by the finding of Fossa and associates that the different treatment protocols (PVB, PEB, single-agent platinum) did not lead to significantly different results in terms of 3-year progression-free survival, at least within this data set. However, the crucial question for the treatment of metastatic seminoma presently is: what would be the optical treatment protocol for the three different prognostic categories?

1. Good prognosis patients

This group represents 46% of the whole patient population (Table 2) with a 3-year PFS as high as 97%. This result cannot be much improved; it is, however, worthwhile to investigate whether the same result could be achieved by a less toxic treatment, e.g. single-agent carboplatin.

In particular, the final results of the two randomised studies addressing this question (MRC trial, PE versus single-agent carboplatin, 130 patients, closed; German AIO trial, PE versus single-agent carboplatin, > 200 patients, ongoing) must be analysed according to the prognostic models proposed by the MRC group; this analysis will be able to define whether there is a subgroup of patients which is sufficiently treated by single-agent carboplatin and which patient should be treated with cisplatin-combination chemotherapy.

2. Intermediate prognosis group

This group represents 27% of the patients with advanced seminoma with a 3-year PFS of 86%. The prognosis of these patients is clearly impaired in comparison with the good prognosis group and deserves further improvement; if this cannot be achieved at least the possibility of achieving the same result with less toxicity deserves investigation.

3. Poor prognosis group

A relatively large proportion of patients with advanced seminoma (27%) have a relatively poor prognosis of 56% PFS after 3 years. This prognostic category clearly identifies a group of patients for whom better treatment options are definitely necessary. These patients should not be included within clinical trials designed for good risk testicular cancer, such as the current EORTC/MRC trial; they should rather be treated according to protocols designed for poor-risk NSGCT with more aggressive regimens, e.g. including high-dose chemotherapy.

The study by Fossa and associates has some limitations:

- possible selection bias due to the retrospective nature of the data collection, particularly in light of low patient numbers within the different stages and risk groups;
- a relatively high proportion of early stage II A/B (13% of all patients) which are usually not included in 'typical' clinical trials for advanced seminoma and are therefore also not included in the two validation data sets;
- availability of LDH levels in only 49% of the total patient population with a probably unequal, non-random distribution of missing data within the different prognostic categories—in contrast to the validation sets without missing LDH values;
- a relatively large proportion of patients (20%) treated by single-agent carboplatin which is not regarded as standard chemotherapy; furthermore, the majority of these patients belonged to the good prognosis group [9].

However, these possible limitations are of minor concern and it is not very likely that elimination of these factors would have remarkably changed the definition of both prognostic models. A further validation of these models could be the current German study which used some of the relevant prognostic factors for stratification: LDH, NPVM, prior irradiation. Presently, these prognostic models presented in the excellent publication from Fossa and associates are very useful. It is very unlikely that more detailed clinical parameters could improve the power of the prognostic models, but it might be worth prospectively investigating in the future some of the biological parameters listed in Table 3. Of particular

Table 2. Comparison of the proportion of patients and their prognosis within the three different prognostic models for metastatic seminoma

	Prognostic models		
	MRC model 1	MRC model 2	IGCCCG
Proportion of patients			
good prognosis	46%	81%	90%
intermediate prognosis	27%	—	—
poor prognosis	27%	19%	10%
Progression-free survival (at 3 years)			
good prognosis	97%	94%	82%
intermediate prognosis	86%	—	—
poor prognosis	56%	56%	67%

Table 3. Investigational prognostic factors for early and late stage seminoma

Low molecular weight (pre)ceratin (atypical seminoma)
MHC class I expression (atypical seminoma)
DNA index; S-phase fraction
Placental alkaline phosphatase level
Neuron-specific enolase level
N-ras point mutation (codon 12)
n copies i 12p
EGF receptor expression
Membraneous C-Kit expression
Hst-1/K-FGF expression
IGF I/II expression
Apo-1/FAS expression
bcl-2/bax ratio

interest might be parameters indicative of a proliferative potential [13], 'atypical' seminoma and platinum resistance [4, 8].

It might be a reasonable approach in the future to combine clinical as well as molecular biological parameters; such a combined model could have the potential to predict even more precisely the prognosis of an individual patient and to guide the treatment decision for a more individualised management of patients with advanced seminoma.

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